Crotaline Fab Antivenom for the Treatment of Children With Rattlesnake Envenomation

Steven R. Offerman, MD*‡; Sean P. Bush, MD§; James A. Moynihan, MD§; and Richard F. Clark, MD*‡

ABSTRACT. *Objective.* **There is little data regarding safety or efficacy of Crotalinae polyvalent immune Fab (ovine) antivenom (crotaline Fab) in pediatric patients. Our objective was to provide the first information regarding safety and effectiveness of this new drug in children.**

Methods. **Data were collected prospectively and retrospectively for all consecutive pediatric patients bitten by rattlesnakes and treated at 2 urban hospitals during 2001. Cases were included if there were signs of envenomation at presentation, patient age was 13 years or less, and there was administration of crotaline Fab. Cases were excluded if antivenin (Crotalidae) polyvalent (equine origin, the conventional antivenom) was given. Primary outcome variables were snakebite severity scores throughout the course of therapy, number of vials of crotaline Fab administered, occurrence of allergic reactions, adjunct surgical therapy, and the presence of permanent sequelae or serum sickness identified at follow-up.**

Results. **In the 12 cases studied, ages ranged from 14 months to 13 years (mean: 6.9; standard deviation: 4.2). Presentation snakebite severity scores ranged from 2 to 9 (mean: 5.3; standard deviation: 2.3). Total crotaline Fab doses ranged from 4 to 22 vials (mean: 12.7; standard deviation: 5.4). Initial control of symptoms was achieved with 4 to 16 vials (mean: 7.7; standard deviation: 3.7), and severity scores stabilized or improved within 24 hours in all patients. Recurrence of local swelling occurred in 1 case despite scheduled repeat doses of antivenom. No cases required surgical intervention, and no permanent sequelae were identified. No immediate or delayed hypersensitivity reactions occurred.**

Conclusion. **In this group of pediatric patients treated for rattlesnake envenomation, crotaline Fab antivenom was safe and seemed to be effective.** *Pediatrics* **2002;110: 968–971;** ***rattlesnake, envenomation, pediatric, treatment, antivenom.***

ABBREVIATIONS. Crotaline Fab, Crotalinae polyvalent immune Fab (ovine) antivenom; ACP, antivenin (Crotalidae) polyvalent; SD, standard deviation.

From the *Division of Medical Toxicology, Department of Emergency Medicine UCSD Medical Center, San Diego, California; ‡San Diego Division of California Poison Control System, San Diego, California; §Department of Emergency Medicine, Loma Linda University School of Medicine, Medical Center and Children's Hospital, Loma Linda, California.

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Reprint requests to (R.F.C.) 200 W Arbor Dr, San Diego, CA 92103-8925. E-mail: rfclark@ucsd.edu

Although >4000 snakebites were reported to the American Association of Poison Control Centers in 2000,[1] it is estimated that >7000 venomous snakebites may actually be treated in the United States annually.[2–5] Crotaline species (pit vipers), including rattlesnakes, copperheads, and cottonmouths, are responsible for the vast majority of venomous bites requiring treatment. Children have been estimated to represent ~20% of rattlesnake envenomations,[3,5–7] but poison center data suggests over 50% of all reported cases may involve pediatric patients.[1] Antivenom therapy is generally considered to be the standard of care for treatment of crotaline-envenomated patients regardless of age.

In December 2000, a new product, Crotalinae polyvalent immune Fab (ovine) antivenom, (crotaline Fab; CroFab, Protherics Inc, Nashville, TN) became available commercially. This antivenom preparation has been shown in initial studies to be effective and approximately 5 times as potent as the previously available antivenom formulation, ACP (antivenin [Crotalidae] Polyvalent , Wyeth-Ayerst Pharmaceuticals, Philadelphia, PA).[8–11] The recent introduction of this new product and pending withdrawal of the traditional antivenom from the market has changed the way rattlesnake envenomation is treated in all populations. In some hospitals, crotaline Fab may already be the only antivenom available. Nevertheless, there is little data regarding its safety or efficacy in pediatric patients. Until now, the safety of this product in children has been inferred based on adult trials, previous experience with digoxin Fab, and the older whole-antibody antivenom.[12] Our objective was to provide data regarding safety and effectiveness of this drug in children.

METHODS

Data were collected prospectively at one center and retrospectively at a second center for all consecutive children bitten by a rattlesnake who presented during 2001. Pediatric age was defined as 13 years or younger. Patients were included in the study if there were symptoms of crotaline envenomation at presentation and antivenom therapy was administered. Patients were excluded if ACP was given at any time during the course of therapy. In those cases where chart review was performed, nursing as well as physician notes were reviewed for data abstraction. Data for each study patient was transferred to a standardized data sheet and analyzed. Primary outcome variables included snakebite severity scores, need for surgical therapy, presence of sequelae at follow-up, and hypersensitivity reactions to antivenom dosing. Additional data collected included the patient's age, sex, location of bite, time to presentation, total number of vials of crotaline Fab antivenom administered, number of vials needed to stabilize symptoms, fibrinogen and platelet levels during hospitalization, and snakebite severity scores[13] recorded at multiple intervals dur-

ing hospitalization. Follow-up data regarding recovery from local effects, permanent disability, and antivenom complications was collected by the authors either by emergency department recheck examination or telephone for all patients. Follow-up was obtained by recheck examination at 1 month after discharge when possible, telephone follow-up was conducted at some time after 1 month in all other cases. Descriptive statistics including mean, median, range, and standard deviation (SD) were calculated for data analysis. This study was approved by the institutional review boards at both institutions.

"Initial control" was defined as the arrest of progression of signs and symptoms for at least 6 hours of any and all components of the envenomation syndrome (no additional advancement of swelling, resolution of systemic effects, and improving coagulopathy). After initial control was achieved, additional antivenom was given in accordance with recommendations in the package insert if the treating physician and envenomation specialist judged it to be indicated. At each time interval for each patient, we calculated the snakebite severity score, a validated quantification of envenomation based on limb swelling; coagulation tests; and neurologic, cardiovascular, pulmonary, and gastrointestinal symptoms and signs.[13] "Scheduled dosing" refers to administration of crotaline Fab every 6 hours for 3 doses (as recommended in the prescribing information).

Similar poisonous snake species are found in the regions of the 2 study centers. The primary indigenous species are all rattlesnakes and include the southern Pacific rattlesnake (*Crotalus helleri*), red diamond rattlesnake (*Crotalus ruber*), speckled rattlesnake (*Crotalus mitchelli*), sidewinder (*Crotalus cerastes*), western diamondback (*Crotalus atrox*), and Mojave rattlesnake (*Crotalus scutulatus scutulatus*). Data regarding the exact snake species involved was frequently not available and therefore not specifically collected for this study. When identification was made, a notation was recorded on the data sheet.

Both of the study centers serve as regional transfer centers for snakebite, each possessing a qualified consultation service that supervises the treatment of all envenomations. At both locations, crotaline Fab has been used as the antivenom of choice since before the 2001 snakebite season. Similar treatment strategies are used by the consultation services for each hospital.

RESULTS

Sixteen pediatric rattlesnake envenomations were treated at the study centers during 2001. Four patients were excluded from the analysis, leaving 12 study patients. Of the excluded patients, 3 were given ACP and 1 was treated without antivenom. All patients in this series were bitten by locally indigenous rattlesnakes. The 12 study patients ranged in age from 14 months to 13 years (mean: 6.9; SD: 4.2). Half were male and half female. Hospital presentation times ranged from 15 minutes to 23 hours (mean: 3.41 hours; SD: 6.27). Seventy-five percent of the snakebites were located on the upper extremity and 25% on the lower extremity. Snakebite severity scores on presentation ranged from 2 to 9 (mean: 5.3; SD: 2.3). Data were collected prospectively for 9 patients and retrospectively for 3 patients (Table 1).

Symptoms were stabilized or improved in all patients at the 6-hour assessment. Severity scores stabilized or improved within 24 hours in every case. In 1 patient, recurrence of local swelling was observed at the 12-hour assessment despite an initial response to crotaline Fab and repeated dosing. At the 24-hour assessment, this child's swelling had improved, and no additional recurrence was observed (Table 1). Abnormal coagulation laboratory values were noted at presentation in 2 cases. One patient presented with a fibrinogen of <20 mg/dL. Another presented with a fibrinogen of 40 mg/dL and platelets of 40 000/high-powered field. All of these laboratory abnormalities resolved after antivenom therapy. Another patient with normal platelet levels throughout her hospitalization was found to have a count of 128 000/high-powered field just before hospital discharge on day 3. No additional antivenom was administered, and no laboratory tests were repeated. On telephone follow-up, this patient was found to have no complications after discharge.

No patients required surgical intervention. No permanent sequelae were identified at hospital discharge or follow-up. No immediate or delayed hypersensitivity reactions were detected after antivenom administration or at follow-up evaluations.

DISCUSSION

The 12 children presented here suffered rattlesnake envenomation and were treated with crotaline Fab antivenom. In all cases, control of envenomation symptoms was achieved with crotaline Fab, and outcomes were satisfactory. There was no evidence of acute or delayed hypersensitivity in this series.

The use of antivenom therapy for the treatment of crotaline (previously termed "crotalid") envenomation in the United States dates back to the early 1950s. Although there has never been a controlled human

TABLE 1. Pediatric Patients' Snakebite Severity Scores After Rattlesnake Bite and Treatment With Crotaline Fab Antivenom

Patient Number	Age	M/F	Initial Control Dose (Vials)	Subsequent Dosing (Vials)	Total Dose (Vials)	Snakebite Severity Score			
						Presenting	6 Hours	12 Hours	24 Hours
1	14 mo	F	12	2 every 6 h × 3 doses	18	6	4	4	2
2	2 y, 7 mo	M	6	2 every 6 h × 3 doses	12	3	3	3	2
3	2 y, 10 mo	F	16	2 every 6 h × 3 doses	22	8	4	4	2
4	5 y	F	6	2 every 6 h × 3 doses	12	5	5	4	3
5	7 y	F	6	2 every 6 h × 3 doses	12	4	2	1	1
6	9 y	F	6	2 every 6 h × 3 doses	12	9	1	1	1
7	10 y	M	6	2 every 6 h × 5 doses	16	4	3	4*	3
8	11 y	M	6	2 every 6 h × 3 doses	12	2	2	2	2
9	13 y	M	12	2 every 6 h × 3 doses	18	5	2	2	2
10†	18 mo	M	8	2 at 6 h	10	5	2	2	1
11†	11 y	F	4	None	4	2	2	2	2
12†	8 y	M	4	None	4	4	1	1	1
Mean (±SD)	6.9 (±4.2)		7.7 (±3.7)		12.7 (±5.4)	5 (±2.3)	2.6 (±1.2)	2.5 (±1.2)	1.8 (±0.7)
Range	14 mo to 13 y		4 to 16		4 to 22	2 to 9	1 to 5	1 to 4	1 to 3

* Local recurrence.
† Retrospective data.

study demonstrating efficacy of antivenom, its use has become the standard of care based on animal data,[14–17] observational studies,[3,5,18] and case reports.[19–21] Until recently, the only antivenom preparation available in the United States was a horse serum derivative with a high incidence of acute and delayed hypersensitivity reactions.[22] Concerns regarding side effects have created controversy regarding the exact indications for antivenom therapy after snakebite and caused past authors to urge caution in both adult[22,23] and pediatric populations.[24,25]

Crotaline Fab is extracted from pooled ovine serum of flocks inoculated with venom from one of four North American crotaline species: *C atrox*, *Crotalus adamanteus* (eastern diamondback), *C scutulatus scutulatus*, and *Agkistrodon piscivorus* (cottonmouth). Antibodies produced against these venoms are extracted and subjected to papain, which cleaves the larger and more antigenic Fc (crystalline) fragments, enabling their removal. The remaining Fab fragments are affinity purified through a column before lyophilization into the final preparation.[26] The new antivenom preparation has been created in an attempt to make a more potent and less antigenic antidote.

In rodent studies, crotaline Fab proved to be 5 times as potent as ACP.[8] Initial human studies in 38 patients older than 10 years of age demonstrated crotaline Fab to be safe and effective.[9,27] In the most recent published series of 28 patients treated for rattlesnake envenomation, crotaline Fab again seemed to be effective.[28] No acute hypersensitivity reactions occurred. However, 2 patients did report mild symptoms of serum sickness after discharge and were easily treated with diphenhydramine. Although this study provides no control arm, these results seem to demonstrate an improvement in the side effect profile for crotaline Fab over ACP. Acute hypersensitivity reactions seem to be less severe and occur less frequently than with ACP. The exact incidence of serum sickness associated with crotaline Fab is unknown, as several of the reported cases may have been related to a single impure lot of antivenom.[26,29]

A concerning phenomenon observed in both of the above mentioned studies was the recurrence of local and hematologic toxicity after initial improvement.[8,28] This phenomenon may be attributable to the rapid clearance of crotaline Fab in the face of retained venom at the envenomation site.[27] Although recurrence may not be unique to crotaline Fab,[30] recent recognition has led toxicologists to recommend close monitoring of patients after crotaline Fab therapy.[27,28]

Our series of 12 children treated for rattlesnake envenomation suggests that the use of crotaline Fab is safe and effective in this population. In no case was surgical therapy necessary. There was no permanent morbidity or mortality associated with the envenomations and no complications from Fab antivenom therapy. Snakebite severity score was stable or decreased at the 6-hour assessment in all cases.

In 1 case, recurrence of local swelling was observed 12 hours after treatment despite repeat scheduled doses of antivenom. Although previous data failed to find any recurrence with scheduled dosing of antivenom,[31] a recent case series suggests that recurrence may occur despite recommended repeated dosing.[28] Because the exact incidence and time course of recurrence has not yet been determined, patients treated with crotaline Fab require close observation and frequent assessment for the return of swelling or coagulopathy for at least the first 24 hours after envenomation. Additional crotaline Fab should be administered as soon as recurrence is observed.

When one administers crotaline Fab, some issues unique to pediatric patients should be considered. In this series, crotaline Fab doses were not adjusted based on patient weight or age. Antivenom dosage should reflect venom load rather than patient size and is therefore based on the severity of signs and symptoms of envenomation. The crotaline Fab package insert recommends dilution of the antivenom in 250 mL of normal saline with administration over 1 hour. This volume of fluid is generally not a problem in children as it approximates a typical fluid bolus in a toddler. However, fluid volume adjustments may be necessary in very small patients (<10 kg). It should also be noted that the current crotaline Fab antivenom formulation contains thimerosal.[26] Although the long-term health risks of this mercury-containing preservative may still be debated, the current evidence suggests that the risks of untreated rattlesnake envenomation far outweigh the risks associated with thimerosal exposure.[32]

Although this series includes a small number of patients, these early results imply that crotaline Fab is safe and effective in children. Larger, controlled pediatric studies are necessary to confirm our experience. As the use of this antidote becomes more widespread, this data will likely become available. Because some of our data were collected retrospectively, recording bias is a potential limiting factor. It is, however, unlikely that any important morbidity, outcomes, or complications would remain undetected at long-term follow-up.

CONCLUSION

In this small series of patients age 13 or younger treated for rattlesnake envenomation, the use of crotaline Fab antivenom was safe and seemed to be effective. Our data supports the use of this new antivenom for children bitten by rattlesnakes.

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